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Huntington Disease in Maryland: Clinical Aspects of Racial Variation

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SUMMARY

In a Maryland survey of Huntington disease, the prevalence in blacks was unexpectedly high and equal to that in whites. Age at onset was earlier in blacks, and their clinical features, at all ages at onset, were similar to those seen in juvenile-onset Huntington disease. Blacks had more severe bradykinesia and abnormalities of eye movement and less frequent psychiatric disorder, particularly depression.

INTRODUCTION

According to several case reports and three surveys, Huntington disease (HD) is rare in native Africans and less prevalent in mixed-race blacks (hereafter referred to as "blacks") than in whites (Bower et al. 1890; Dercum 1891; Burr 1921; Gordon 1935–36; Stone and Falstein 1939; Hutton 1956; Reed and Chandler 1958; Beaubrun 1962; Klintworth 1962; Haddock 1973; Harries 1973; Osuntokun 1973; Saffer et al. 1974; Hayden and Beighton 1977; Still 1977; Samuels and Gelfand 1978; Glass and Saffer 1979; Hayden 1979; Barnes and Hein 1981; Wright et al. 1981; Hayden et al. 1982). However, because HD is thought to be uncommon in blacks, it is not usually part of the differential diagnosis of movement disorder in blacks, so that only cases with typical manifestations are likely to be diagnosed and thereby reported. Further underreporting could result from the unavailability of family-history information in many black patients.

In those native Africans and blacks who have been reported, the age at onset

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is usually younger than average, although this was not found in the only systematic American survey that specifically attempted to find blacks with HD (Wright et al. 1981). Therefore, the early age at onset of reported black cases may also be secondary to reporting bias. Cases of blacks with early onset of HD are considered particularly unusual and may be preferentially reported.

The clinical features in blacks with HD have not been reported. It would be of interest if blacks, as a group, had an earlier onset than whites and an unusual phenotype, suggesting either another HD allele or a gene modifier that is prevalent in blacks.

In a survey of HD in Maryland during 1980–83, we found an unexpectedly large number of black cases, providing us with an opportunity to compare the prevalence and clinical manifestations of HD in representative samples of American blacks and whites. We found a much higher than expected prevalence of HD in blacks but confirmed the early age at onset in blacks. In addition, blacks with HD tended to have more severe limitation of eye movements, more severe bradykinesia, and less frequent psychiatric disorder than did whites with HD.

METHODS

Ascertainment

Sources of ascertainment included persons and agencies or institutions that may have been providing care or services to HD patients. To reach patients not registered with any source of care, media announcements were used to publicize the project and its services. The sources of ascertainment and the number of cases found to meet our diagnostic criteria are listed in table 1.

TABLE 1

CASES OF HD DIAGNOSED BY EACH SOURCE

Source	Total No. of Cases (White/Black) Diagnosed by Source	Total No. of Cases (White/Black) Diagnosed Only by Source
General hospital discharge diagnosis	42 (31/11)	6 (6/0)
Johns Hopkins discharge diagnosis	35 (29/6)	1 (0/1)
Johns Hopkins Genetic Clinic[a]	36 (33/3)	0
Urban medical specialists	22 (14/8)	8 (5/3)
Rural physicians	13 (9/4)	3 (2/1)
National Institutes of Health	5 (5/0)	1 (1/0)
County health departments	6 (4/2)	4 (3/1)
Department of social services[b]	16 (7/9)	1 (1/0)
State mental hospitals	12 (8/4)	1 (1/0)
Veterans Administration hospitals	21 (16/5)	9 (6/3)
Nursing homes	17 (16/1)	2 (1/1)
Voluntary health organizations[a]	46 (43/3)	8 (7/1)
Radio and newspaper spots[a]	28 (27/1)	9 (6/3)
Pedigree screening[b]	98 (62/36)	45 (28/17)

[a] Lower proportion of blacks than whites ascertained by the source.
[b] Higher proportion of blacks than whites ascertained by the source.

Diagnosis

Subjects who were alive and resided in Maryland on April 1, 1980, and who had characteristic motor signs of HD were included. Our diagnostic criteria for *definite HD* were (1) chorea or the characteristic impairment of voluntary movement that was delayed and insidious in onset and that gradually worsened with time and (2) a family history of at least one other family member with these typical features of HD (Folstein et al. 1983*b*, 1986). Diagnostic criteria for *probable HD* were the same, except that the family history was uncertain because of adoption or unknown paternity. Subjects who, after thorough genealogical investigation, had negative family histories were excluded. Dementia and emotional symptoms, although frequent, were neither required nor sufficient for diagnosis.

Clinical Evaluation

All living subjects reported by any source as having HD were examined. The evaluation included detailed documentation of the family history that utilized interviews with relatives, reviews of medical records of affected relatives, and examinations of other consenting family members. Using the family informant who lived with the patient at the time of onset, we documented the year of onset of a movement disorder and the year of onset of major affective disorder when present. To increase the accuracy of estimating age at onset, we used a semistructured interview that helped the informant put symptoms in the context of documented life events.

The examination also included documentation of the patient's medical history, with emphasis on the nature of onset and course of symptoms. If another diagnosis appeared to be more likely than HD, appropriate workup was carried out (Folstein et al. 1986).

A quantitated neurologic examination (the QNE) was designed to document the presence and severity of motor signs seen in HD. The QNE includes 48 items ordinarily used in a clinical neurological examination that have high interrater reliability and discriminate between HD patients and normal controls (Folstein et al. 1983*b*). Two aspects of the QNE that differed in blacks and whites were bradykinesia and eye-movement abnormalities. Bradykinesia is a global rating of spontaneous speed of movement and speech and of the latency between the examiner's request and the initiation of motor performance or speech. The possible scores are as follows: 0, normal speed; 1, mildly slow; 2, moderately slow with significant latency in all performances; and 3, severe bradykinesia with little spontaneous movement and long latency between a comprehended request and intended response. For 20 patients rated by two experienced examiners, the interobserver agreement on this rating was 90%.

Eye movements were scored as follows on 10 separate items: 0, normal; 1, abnormal but present; and 2, no movement. The items are smoothness of horizontal and vertical pursuit, range of motion of horizontal and vertical eye movement, speed of saccadic (voluntary) eye movements, eye blinking with saccades, obligatory head movement with saccades, ability to hold lateral gaze,

and ability to close the eyes on command (Leigh et al. 1983). The scores on these items are highly intercorrelated and were summed to make a total eye-movement score. Interobserver agreement on the individual items ranged from 50% to 100%; for eight of 10 items there was ≥80% agreement.

Psychiatric diagnosis was based on standard DSM-III criteria (DSM III 1980), with one modification: an episode of depression was called major depression only if it lasted ≥1 mo and was not associated in time with the diagnosis of HD, divorce, loss of job, or death of a family member (Folstein et al. 1983*a;* Folstein and Folstein 1983). To systematically elicit symptoms, a structured psychiatric interview, the Diagnostic Interview Schedule (Robins et al. 1981), was administered by an experienced clinician to the patient and a family informant; but it was never the sole source of information. Diagnosis was based on all available information, often including longitudinal follow-up—and, in a few cases, on a review of records only. We report cumulative lifetime prevalence of psychiatric disorder up to the time of the patient's last examination.

Data Analysis

Several of the outcomes on which blacks and whites were compared are strongly influenced by duration of illness, sex of affected parent, and age at onset. Analyses of these variables were carried out using multiple regression to measure the impact of each factor when others were taken into account. Of the 61 black cases, 29 came from one large kindred (Folstein et al. 1984, 1985). All analyses were carried out twice, once including and once excluding this kindred. Reported racial differences in clinical features are those that were equally significant in both analyses and include the large kindred.

RESULTS

Ascertainment

Blacks were rarely ascertained through the Hopkins Genetics Clinic, voluntary health organizations, or media announcements and were more likely than whites to be found through the Department of Social Services and by pedigree screening (table 1). Forty-five cases were ascertained only through pedigree screening of known cases. For half of these, diagnosis was known but not reported, and in the other half a different diagnosis had been made (Folstein et al. 1986). Blacks were twice as likely as whites to go unreported because of misdiagnosis ($\chi^2 = 4.194$, $P = .046$).

Prevalence

Two hundred seventeen persons were found who met our diagnostic criteria for HD, were living in Maryland, and had motor symptoms on April 1, 1980. Two hundred twelve met criteria for definite HD, and five met criteria for probable HD. The point prevalence of HD was estimated at 5.15/100,000 based on a population of 4,217,000. This number is similar to point-prevalence estimates in other HD populations of Western-European origin (Reed and Chandler 1958; Wallace 1972; Mattson 1974; Hayden and Beighton 1977; Wright et al. 1981) (table 2). However, the prevalence in Maryland blacks was much higher

TABLE 2

PREVALENCE OF HD PER 100,000 TOTAL POPULATION

Location (Reference), Prevalence Day	Overall (White/Black) Prevalence
Maryland (Present Study), 4-1-80	5.15 (4.94/6.37[a])
Australia (Wallace 1972), 1-1-69	6.3
Sweden (Mattsson 1974), 7-1-65	4.7
Lower Michigan (Reed and Chandler 1958), 4-1-40[b]	4.12 (4.23[c]/1.44[a])
South Carolina (Wright et al. 1981)	(4.8/0.97[a])
South Africa (Hayden 1979)	(2.22/2.11[d]) (.../0.01[e])

[a] American blacks, generally estimated to have ⅓ "Caucasian-origin" genes, on average (Neel and Schull 1954).
[b] Date is 15 years prior to the investigation of cases.
[c] Estimated from data.
[d] "Colored" or mixed-race blacks.
[e] Africans, without known admixture with Caucasians.

than expected (6.37/100,000) and did not differ appreciably from that found in whites. Even if the large black kindred that accounted for half the black cases was removed, the prevalence (3.34/100,000) would be higher than those in previously reported surveys of mixed-race blacks.

Age at Onset of Motor Symptoms

The mean age at onset of motor symptoms in the Maryland sample was 40.25 years. Motor symptoms began significantly earlier in blacks than in whites (36.2 vs. 41.8 years; $P = .008$), and there was a higher proportion of cases with juvenile (<20 years) onset among the black population (table 3). Our reported age at onset in whites is similar to that of the only other survey (Heathfield 1967) that documented the use exclusively of motor symptoms to designate age at onset, and the age at onset for Maryland blacks is similar to the age at onset for the combined case reports in blacks (table 4).

The effect of paternal transmission on the age at onset in HD has been well

TABLE 3

RACE-SPECIFIC AGE AT ONSET OF MOTOR SYMPTOMS

Parameter	White ($N = 156$)	Black ($N = 61$)	Total ($N = 217$)	P[a]
Mean ± SD age at onset	41.85 ± 12.7	36.20 ± 12.6	40.25 ± 12.9	.008
No. of cases (%) with juvenile (age <20) onset	8 (5.9)	7 (11)	15 (7.9)	.09; $\chi^2 = 2.75$
Mean ± SD age at onset for juvenile cases	14.28 ± 5.5	16.00 ± 3.8	15.14 ± 4.6	.5113

[a] White vs. black.

TABLE 4

REPORTS OF HD IN BLACKS

Location (Reference)	*N*	Mean Age at Onset[a]
United States (Bower and Mills 1890)	1	30
United States (Dercum 1891)	3	12
United States (Barnes and Hein 1918)	1	22
United States (Burr 1921)	1	...
East Africa (Gordon 1936)	1	32–45
United States (Stone and Falstein 1939)	3	40s
Uganda (Hutton 1956)	1	...
Michigan (Reed and Chandler 1958)	3	...
Trinidad (Beaubrun 1962)	...	...
South Africa (Klintworth 1962)	4	...
Ghana (Haddock 1973)	"Rare"	...
Kenya (Harries 1973)	2	27
Nigeria (Osuntoken 1973)	3	...
South Africa (Saffer et al. 1974)[b,c]	5	14.5
South Africa (Hayden 1979)	70	33.5[d]
United States (Still 1977)	5	27[e]
Rhodesia (Samuels and Gelfand 1978)	4	12.5
South Africa (Glass and Saffer 1979)[b]	2	47
South Carolina (Wright et al. 1981)[f]	8	41.8[g]
Total cases with age at onset given	98	...
Mean age at onset of all cases	...	31.5

[a] Criteria varied.
[b] Included in Hayden's sample; not used for our calculation of mean age at onset for all cases.
[c] One-fifth of cases reported had adult onset at unknown age; age at onset given for four juvenile-onset cases.
[d] SD = 1.59.
[e] SD = 5.0.
[f] Does not overlap with Still's cases.
[g] SD = 4.33.

documented (Merritt et al. 1967; Jones and Phillips 1970; Bird et al. 1974; Newcombe et al. 1981). In the Maryland sample, maternally transmitted cases had a later age at onset, by an average of 8 years, than did paternally transmitted cases (table 5). This difference was approximately the same for blacks and whites. The effect of race on age at onset persisted ($P = .0377$) after paternal transmission was taken into account by means of multiple regression analysis.

TABLE 5

RELATIONSHIP BETWEEN AGE AT ONSET AND SEX OF AFFECTED PARENT

	MEAN ± SD AGE AT ONSET		
RACE (*N*)	Maternal Transmission	Paternal Transmission	*P*[a]
White (156)	45.7 ± 12.2	38.1 ± 12.3	.000
Black (61)	40.4 ± 9.9	32.4 ± 13.7	.02
Total (217)	44.3 ± 11.8	36.4 ± 12.9	.000

[a] Significance of the difference.

Duration of Illness

Since prevalence determination day, 50 of the patients ascertained and living in Maryland have died. The mean duration of illness (from estimated year of onset to year of death) was 15.16 years (SD = 9.0, SE = 1.27), a finding similar to that of earlier reports (Reed and Chandler 1958; Bruyn 1968). The mean duration was essentially the same for whites and blacks, 15.03 and 15.63 years, respectively.

Neurological Findings

Race had no overall effect on the patients' scores on the chorea and motor-impairment scales of the QNE, scores that were most powerfully predicted by duration of illness at the time of examination.

Bradykinesia was found to be more severe in blacks (P = .0306), when regression analysis was used to account for the effect of duration of illness. Blacks also tended to have more abnormalities of eye movements than did whites (P = .09). In retrospect, these findings corresponded to our clinical experience with the black patients, but they were not predicted. Neither bradykinesia nor eye-movement scores were significantly related to age at onset, after race and duration of illness were taken into account. The increased rates of bradykinesia and abnormal eye movements in blacks were not accounted for by the juvenile-onset cases but were present in black cases of all ages at onset.

Psychiatric Disorder

We were able to obtain adequate psychiatric information for 186 cases. The most prevalent disorders (table 6) were major affective disorder, 32.8%; alcoholism, 15.6%; and intermittent explosive disorder, 30.6%. The lifetime prevalence of major affective disorder was 4.3% in a local community survey carried out concurrently with the HD survey and using similar diagnostic criteria. The rate of alcoholism was not different from that in the community sur-

TABLE 6

DISTRIBUTION OF PSYCHIATRIC DISORDER IN BLACK AND WHITE HD SUBJECTS

DSM III DIAGNOSIS	No. (%) OF SUBJECTS WITH DIAGNOSIS		
	Black (N = 50)	White (N = 136)	Total (N = 186)[a]
None	23 (46.0)	33 (24.3)	56 (30.1)[b]
Affective disorder	5 (10.0)	56 (41.2)	61 (32.8)[b]
Dsythymic disorder	5 (10.0)	4 (2.9)	9 (4.8)
Intermittent explosive disorder	10 (20.0)	47 (34.6)	57 (30.6)[b]
Alcoholism	9 (18.0)	20 (14.7)	29 (15.6)
Schizophrenia	1 (2.0)	7 (5.2)	8 (5.9)
Antisocial personality	5 (10.0)	6 (4.4)	11 (5.9)
Other	4 (8.0)	15 (11.0)	19 (10.2)

[a] Totals exceed the number of patients because a number of patients met criteria for more than one DSM III diagnosis.

[b] Racial difference in proportions significant at $P < .05$.

vey; intermittent explosive disorder was not reported (Robins et al. 1984). There was a marked racial difference in the lifetime prevalence of psychiatric disorder in the HD population that was not found in the community survey. Blacks had less major affective disorder, less explosive disorder, and less psychiatric disorder overall.

The age at onset of motor symptoms for persons with affective disorder was significantly later than that for persons without affective disorder, 43.4 years and 38.7 years, respectively ($t = 2.24$, $O = .03$). These differences were present in both races but did not attain statistical significance because there were so few observations of major affective disorder in blacks.

DISCUSSION

Prevalence

Two hundred seventeen patients with HD were ascertained in a survey of Maryland. Contrary to our expectations, the overall prevalence and the prevalence in whites were not different from those reported in other surveys, which preceded the recent public education about HD. However, the prevalence in blacks was much higher than previously reported. There are several possible reasons for this unexpected finding. First, the black cases may have a different condition. However, the diagnosis was confirmed by autopsy in seven of the black kindreds, accounting for 40 of the 61 cases, and two kindreds showed linkage to the G8 probe (Folstein et al. 1985; Koven et al. 1986). Second, the incidence may be increasing in blacks. Black families tend to be large, so that once the gene has been introduced into the black community, one would expect the number of new cases of HD to increase at a faster rate than it does in the white population. However, this should not increase either the overall or the black prevalence. More likely, previous surveys have underestimated prevalence in blacks. Misdiagnosis has been frequent, partly because HD is not expected in blacks and partly because genealogies are difficult to obtain. Also, the clinical presentation in blacks is somewhat different from that in whites, making diagnosis more difficult (Koven et al. 1986).

Is the high prevalence in blacks compatible with the assumption that HD in blacks is due entirely to racial admixture? Even though the black HD families were of mixed race, in only one of the 23 kindreds did we document a Caucasian origin of the HD gene. Although documentation was sometimes fragmentary, many of our black genealogies were extensive. An HD mutation may have been brought from Africa. HD has been reported in African blacks from several countries since 1935 (see Wright et al. 1981 for review). Hayden systematically surveyed South Africa in 1979 and found 11 African HD cases for whom white ancestry was highly unlikely. Because his access to cases was limited, the prevalence (0.6 cases/1,000,000) was likely to be an underestimate; but it can be concluded that HD exists in Africans.

Clinical Differences in Black and White HD Patients

When the 61 black patients were compared with the 156 white patients, blacks were found to have an earlier mean age at onset. Hayden found the same

differences in his survey of South-African Caucasians and mixed-raced blacks. On examination, Maryland blacks with HD had more severe bradykinesia and eye-movement abnormalities and less psychiatric disorder. These differences could not be accounted for by the contribution of either juvenile cases or one particularly large black family and persisted when concomitant variables such as duration of illness and paternal transmission effect were taken into account.

Possible Genetic Explanations of the Differences

The clinical features that define the black HD phenotype are the same ones seen in whites with juvenile-onset HD: bradykinesia, abnormal eye movements, and a low rate of major affective disorder. This phenotype could represent a mutation of another locus, another HD allele, or an unlinked modifier of a single HD allele that is more prevalent in the black population but also exists in Caucasians. Our current knowledge does not allow a distinction among these possibilities, but some speculations are possible.

A second HD locus is not likely. All families tested thus far have shown linkage to the G8 probe (Gusella et al. 1983; Folstein et al. 1985; Youngman et al. 1985; Haines et al. 1986; Koven et al. 1986), including two black kindreds included in our survey (as reported earlier by Folstein et al. [1985] and Koven et al. [1986]).

Whether the black phenotype is more likely to reflect two alleles at the HD locus or an unlinked modifier depends on whether there is familial aggregation of the phenotype. Age at onset aggregates in HD families to some extent (Wallace and Hall 1972; Went et al. 1983; Farrer and Conneally 1985), but the distribution of age at onset within a family is still broad. Farrer and Conneally (1985) suggested that between-family differences in age at onset were due to the effect of genes influencing longevity in the family. They found a strong positive correlation between age at onset of affected members of a family and the age at death of their unaffected sibs. Their data could not address whether such "longevity genes" might be linked to the HD locus. In an earlier study, we demonstrated familial aggregation of major affective disorder in particular HD families (Folstein et al. 1983*a*). When families were ascertained through an HD proband with bipolar affective disorder (probands with episodes of both mania and depression), the secondary-HD cases were much more likely to have affective disorder than when the family was ascertained through an HD patient without affective disorder. These data suggested the presence of either two alleles or a modifier gene that was tightly linked to the HD locus.

In the present study and that of Farrer and Conneally, the paternal transmission effect on the age at onset appeared to be acting independently of the other factors (in the present study racial factors, in theirs familial factors) influencing age at onset. This feature of HD continues to be confirmed by a variety of investigations, but its cause remains unknown.

In summary, we found a higher prevalence of HD in American blacks than previously had been reported, calling into question our usual assumption (based partly on low prevalence)—that is, that HD in American blacks is entirely accounted for by racial admixture. Clinical features in blacks resemble

those often attributed to juvenile onset but were seen in our black HD population across all ages at onset. Our findings suggest that age at onset of HD is influenced by two independent factors: (1) paternal transmission of the HD gene and (2) a separate factor found commonly in blacks and associated with bradykinesia, abnormal eye movements, and absence of affective disorder.

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REFERENCES

Barnes, F. M., and E. Hein. 1918. Chronic progressive chorea in the negro: a case report. J. Mo. Med. Assoc. **15**:324.

Beaubrun, M. H. 1962. Huntington's chorea in Trinidad. Caribbean Med. J. **24**:45–50.

Bird, E. D., A. J. Caro, and J. B. Pilling. 1974. A sex related factor in the inheritance of Huntington's chorea. Ann. Hum. Genet. **37**:255–260.

Bower, J. F., and C. K. Mills. 1890. Notes on some cases of chorea and tremor. J. Nerv. Ment. Dis. **15**:131–142.

Bruyn, G. W. 1968. Huntington's chorea: historical, clinical and laboratory synopsis. Handbook of Clin. Neurol. **6**:298–378.

Burr, C. W. 1921. A negro with Huntington's chorea. Arch. Neurol. Psychiatry **5**:767–768.

Dercum, F. X. 1891. Adult chorea: clinical lectures delivered at Philadelphia Hospital. Int. Clin. **3**:292–297.

Diagnostic and statistical manual of mental disorders (DSM III). 1980. American Psychiatric Association, Washington, D.C.

Farrer, L. A., and P. M. Conneally. 1985. A genetic model for age at onset of Huntington's disease. Am. J. Hum. Genet. **37**:350–357.

Folstein, S. E., M. H. Abbott, G. A. Chase, B. A. Jensen, and M. F. Folstein. 1983*a*. The association of affective disorder in Huntington's disease in a case series and in families. Psychol. Med. **13**:537–542.

Folstein, S. E., M. H. Abbott, M. L. Franz, S. Huang, G. A. Chase, and M. F. Folstein. 1984. Phenotypic heterogeneity in Huntington's disease. J. Neurogenet. **1**:175–184.

Folstein, S. E., and M. F. Folstein. 1983. Psychiatric features of Huntington's disease: recent approaches and findings. Psychiatr. Devel. **2**:193–206.

Folstein, S. E., B. A. Jensen, J. R. Leigh, and M. F. Folstein. 1983*b*. The measurement of abnormal movement: methods developed for Huntington's disease. Neurobehav. Toxicol. Teratol. **5**:605–609.

Folstein, S. E., R. L. Leigh, I. Parhad, and M. F. Folstein. 1986. The diagnosis of Huntington's disease. Neurology **36**:1279–1283.

Folstein, S. E., J. A. Phillips III, D. A. Meyers, G. A. Chase, M. H. Abbott, M. L. Franz, P. G. Waber, H. H. Kazazian, P. M. Conneally, W. Hobbs, R. Tanzi, A. Faryniarz, K. Gibbons, and J. Gusella. 1985. Huntington's disease: two families with differing clinical features show linkage to the G8 probe. Science **229**:776–779.

Glass, J., and D. S. Saffer. 1979. Huntington's chorea in a black family. South Afr. Med. J. **56**:685–688.

Gordon, H. L. 1936. Huntington's chorea in an East African. Proc. R. Soc. Med. **29**:1469–1470.

Gusella, J., N. S. Wexler, P. M. Conneally, S. L. Naylor, M. A. Anderson, R. E. Tanzi, P. C. Watkins, K. Ottina, M. R. Wallace, A. Y. Sakaguchi, A. B. Young, I. Shoulson, E. Bonilla, and J. B. Martin. 1983. A polymorphic DNA marker genetically linked to Huntington's disease. Nature. **306**:234–238.

Haddock, R. D. W. 1973. Neurological disorders in Ghana. Pp. 143–160 *in* J. D. Spillane, ed. Tropical neurology. Oxford University Press, New York.

Haines, J., R. Tanzi, N. Wexler, P. Harper, S. Folstein, J. Cassiman, R. Meyers, A. Young, M. Hayden, A. Falek, E. Tolosa, S. Crespi, G. Campanella, G. Holmgren, M. Anvret, I. Kanazawa, J. Gusella, and M. Conneally. 1986. No evidence of linkage heterogeneity between Huntington's disease (HD) and G8 (D4S10). Am. J. Hum. Genet. **39**, Suppl.:A156.

Harries, J. R. 1973. Neurological disorders in Kenya. Pp. 207–222 *in* J. D. Spillane, ed. Tropical neurology. Oxford University Press, New York.

Hayden, M. R. 1979. Huntington's chorea in South Africa. Ph.D. thesis, University of South Africa.

Hayden, M. R., and P. Beighton. 1977. Huntington's chorea in the Cape coloured community of South Africa. South Afr. Med. J. **52**:886–888.

Hayden, M. R., J. M. MacGregor, D. S. Saffer, and P. H. Beighton. 1982. The high frequency of juvenile Huntington's chorea in South Africa. J. Med. Genet. **19**:94–97.

Heathfield, K. W. G. 1967. Huntington's chorea: investigation into the prevalence of this disease in the area covered by the North East Metropolitan Regional Hospital Board. Brain **90**:203–232.

Hutton, P. W. 1956. Neurological disease in Uganda. East Afr. Med. J. **33**:209–223.

Jones, M. B., and C. R. Phillips. 1970. Affected parent and age of onset in Huntington's chorea. J. Med. Genet. **7**:20–21.

Klintworth, G. K. 1962. Huntington's chorea in South Africa. South Afr. Med. J. **36**:896–898.

Koven, S. J., R. M. Zweig, S. E. Folstein, N. Maestri, J. G. Gusella, M. L. Franz, and H. H. Kazazian. 1986. An atypical form of Huntington's disease is inherited at the known HD locus. Am. J. Hum. Genet. **39**, Suppl.:A96.

Leigh, J. R., S. A. Newman, S. E. Folstein, A. G. Lasker, and B. A. Jensen. 1983. Abnormal ocular motor control in Huntington's disease. Neurology **33**:1268–1275.

Mattson, B. 1974. Huntington's chorea in Sweden: prevalence and genetic data. Acta Psychiatr. Suppl. **255**:211–219.

Merritt, A. D., P. M. Conneally, N. F. Rahnam, and A. L. Drew. 1967. Juvenile Huntington's chorea. Pp. 645–650 *in* Proceedings of the Second International Congress of Neuro-genetics and Neuro-opthalmology of the World Federation of Neurology. Vol. **1**. A. Barbeau and J.-R. Brunette, eds. Progress in neurogenetics. Excerpta Medica, Amsterdam.

Neel, J. V., and W. J. Schull. 1954. Pp. 230–260 *in* Human heredity. University of Chicago Press, Chicago.

Newcombe, R. G., D. A. Walker, and P. S. Harper. 1981. Factors influencing age at onset and duration of survival in Huntington's chorea. Ann. Hum. Genet. **45**:387–396.

Osuntokun, B. O. 1973. Neurological disorders in Nigeria. Pp. 161–190 *in* J. D. Spillane, ed. Tropical neurology. Oxford University Press, New York.

Reed, T. E., and J. H. Chandler. 1958. Huntington's chorea in Michigan: demography and genetics. Am. J. Hum. Genet. **10**:201–225.

Robins, L. N., J. E. Helzer, J. Croughan, J. B. W. Williams, and R. L. Spitzer. 1981. NIMH diagnostic interview schedule, version III. Developed for the National Institute of Mental Health, Division of Biometry and Epidemiology, under contract MH 278-79-00 17 DB and research grant 33583.

Robins, L. N., J. E. Helzer, M. M. Weissman, H. Orvaschel, E. Gruenberg, J. D. Burke, and D. A. Regier. 1984. Lifetime prevalence of specific psychiatric disorders in three sites. Arch. Gen. Psychiatry **41**:949–958.

Saffer, D. S., D. C. Nathan, P. A. Kahle, B. Steingo. 1974. Huntington's disease in a coloured family. South Afr. Med. J. **48**:2399–2402.

Samuels, B. L., and M. Gelfand. 1978. Huntington's chorea in a black Rhodesian family. South Afr. Med. J. **54**:648–650.

Still, C. N. 1977. Huntington's chorea in South Carolina: natural history and clinical features. Neurol. Neurocir. Psiquiatr. **18**:193–198.

Stone, T. T., and E. I. Falstein. 1939. Genealogical studies in Huntington's chorea. J. Nerv. Ment. Dis. **89**:795–809.

Wallace, D. C. 1972. Huntington's chorea in Queensland: a not uncommon disease. Med. J. Aust. **1**:299–307.

Wallace, D. C., and A. C. Hall. 1972. Evidence of genetic heterogeneity in Huntington's chorea. Neurol. Neurosurg. Psychiatry **35**:789–800.

Went, I. N., M. Vegter-Van der Vlis, G. W. Bruyn, and W. S. Volkers. 1983. Huntington's chorea in the Netherlands: the problem of genetic heterogeneity. Ann. Hum. Genet. **4**:205–214.

Wright, H. H., C. N. Still, and R. K. Abramson. 1981. Huntington's disease in black kindreds in South Carolina. Arch. Neurol. **38**:412–414.

Youngman, S., M. Sarfarazi, P. S. Harper, O. W. Quarrell, D. Shaw, and J. Gusella. 1985. G8 typing of Huntington's disease: families in south Wales. Am. J. Hum. Genet. **37**, Suppl.:A185.